Journal of Pioneering Medical Sciences
Received: October 30, 2024 | Accepted: December 15, 2024 | Published: February 05, 2025
Volume 14, Issue 01, Pages 59-63

DOI https://doi.org/10.47310/jpms2025140108

Early Therapeutic Effect for Local Mild Magnetothermy (Hyperthermy) and Dose-Dense PLD in Comprehensive Treatment of Resistant Breast Cancer

Movchan Oleksii Volodimirovich[1*], Smolanka Ivan Ivanovich[2], Lyashenko Andriy Oleksandrovich[3], Loboda Anton Dmitrovich[4], Ivankova Oksana Mykolaivna[5] and Dosenko Irina Viktorivna[6]

[1-6]Department of Breast Cancer and Reconstructive Surgery, State Non-commercial Enterprise, National Cancer Institute of the Ministry of Health of Ukraine, Kyiv, Ukraine

Author Designation: [1,3,4,5,6]Doctor, [2]Profesor

*Corresponding author: Movchan Oleksii Volodimirovich (e-mail: aleexeymed@gmail.com).

Abstract **Objectives:** Overcoming drug resistance by altering the medication's characteristics and the tumor microenvironment might be a therapy improvement strategy. Newly used is Pegylated Liposomal Doxorubicin (PLD) but is significantly more effective under the Magnetothermy (Hyperthermy) modification. The optimal dose and cycle of PLD-based neoadjuvant chemotherapy for Breast Cancer (BC) have yet to be determined. Magnetothermy (Hyperthermy) is a treatment for Advanced Breast Cancer (ABC) that uses time-varying magnetic fields to create eddy currents, resulting in tumor heating (<40°C). Enhance the therapeutic benefits resulted from the synergistic effect of Pegylated Liposomal Doxorubicin in a dose-dense regimen and Local mild Magnetothermy (Hyperthermy) electromagnetic field effect against chemoresistant advanced breast cancer. **Material and Methods.** The study included forty-three patients with chemoresistant ABC: First group: 23 patients, who received a PLD 50 mg/m^2 and regional inductive mild hyperthermia treatment every four week (standard regimen), second group: 20 patients, who received PLD 50 mg/m^2 and regional inductive mild hyperthermia treatment every two week (dose-dense regimen). **Results:** Patients with chemosensitivity (65.12%) reported significantly greater levels of chemotherapy-related variables compared to those with chemoresistance (34.88%), p = 0.0014. When PLD was given for the second group, chemosensitivity was higher than when given for the first group (15 patients or 75.00% vs 13 patients or 56.52%, respectively p = 0.038). But, when PLD was given for the first group, chemoresistance was higher, than when given for the second group (10 patients or 43.48% vs 5 patients or 25.00%, respectively p = 0.023). **Conclusion:** Achieving a quicker clinical response for chemoresistant ABC with a PLD dose-dense regimen while minimizing side effects and adverse responses. The complex employment of magnetothermy and pegylated liposomal drugs resulted in synergy of their anticancer action, which allowed to devitalize the tumor parenchyma of breast carcinoma.

Key Words Chemoresistant breast cancer, pegylated liposomal doxorubicin, local mild magnetothermy (Hyperthermy), dose-dense regimen

INTRODUCTION

The American Cancer Society demonstrated that 30% of tumors had primary resistance to chemotherapy and around 40% of breast malignancies are resistant to anthracycline antibiotics [1]. Overcoming drug resistance by altering the medication's characteristics and the tumor microenvironment might be a therapy improvement strategy.

A promising solution to this problem is the guided transport of anticancer medications throughout the body utilizing a carrier system (drug microencapsulation) against the backdrop of magnetothermy, which leads to a more profuse entrance of the drug into the tumor cell [2].

In tumor cells that are resistant to cytostatics, the composition of lipid and protein membrane components changes, with a rise in the levels of cholesterol, glycosphingolipids, sphingomyelin and phospholipase D [3].

Anthracyclines have high cardiotoxicity level and remains a major barrier to their use; liposome encapsulation is one

technique aimed at reducing this side effect. The newly used is pegylated liposomal doxorubicin but is significantly more effective under the Magnetothermy (Hyperthermy) modification [4]. Pegylated liposomes are tiny enough (mean diameter of 100 nM) to pass through the damaged blood arteries that supply tumors. Pegylated liposomes additionally mix a porous lipid matrix with an internal liquid buffer system, which maintains doxorubicin hydrochloride encapsulated as long as liposomes remain in the blood circulation [5].

The optimal dose and cycle of PLD-based neoadjuvant chemotherapy for breast cancer (BC) have yet to be determined. According to the aforementioned clinical investigations, PLD is primarily delivered at 15-20 mg/m^2 every two weeks, 25-35 mg/m^2 every three weeks, or 40-45 mg/m^2 every two weeks and 50-70 mg/m^2 every three weeks. Although clinical research on multiple doses and cycles can indicate a definite benefit, establishing the optimal dosage and cycle requires more investigation [6]. Study program that includes a systematic assessment of the effectiveness and side effects of different doses and cycles in the same patient population is critical for making the most sensible use of PLD in neoadjuvant chemotherapy for BC. Furthermore, utilizing PLD within the range will not result in substantial hazardous and side effects and adverse responses in clinical investigations employing high-dosage PLD have not increased significantly. This implies that future clinical trials might attempt adding a tiny dosage to obtain higher efficacy without compromising safety [7].

Non-invasive deep hyperthermia is to use the heat generated by eddy currents created within conductors by a changing magnetic field. The frequency of induction heating may be used as a tool to modify the temperature given to the tissue at various depths, resulting in diverse cancer therapy outcomes [8]. Magnetothermy (Hyperthermy) is a treatment for Advanced Breast Cancer (ABC) that uses time-varying magnetic fields to create eddy currents, resulting in tumor heating (<40°C) and redox alterations. Since electromagnetic radiation may control the anticancer impact of medications through the mechanism of free radicals, the activity of these agents in the tumor region [9]. Magnetothermy (Hyperthermy), which uses a frame applicator, heats tissues with a significant number of blood and lymphatic vessels more than fat tissue. Simultaneously, an electrical component in the applicator's electromagnetic field contributes to the therapeutic benefits. On the basis of the above-mentioned medical and physical principles of magnetothermy, the "MagTherm" device (Radmir, Ukraine) with techniques of complicated therapy for oncological patients, which got clinical approval from the Ministry of Health of Ukraine, was created [10], when implementing new methods and combinations of treatment for this aggressive breast cancer form and thinking of all unfavorable factors that may worsen the final results of treatment. The National Comprehensive Cancer Network guidelines recommended PLD as the first-line treatment for ABC [11].

The ability to achieve hyperthermic temperatures in tumors is beneficial in contemporary magnetic resonance nanotheranostics technologies, which combine magnetic resonance treatment with the use of magnetic nanoparticles as active agents. At the same period, the three-year survival rate for patients was 100% [12].

Doxorubicin-encapsulated pegylated liposomes were developed and evaluated as a novel nanocarrier for treating BC. The results showed that the nanocarrier was approximately 128 nm in size. PEG conjugation in magnetic liposomes was equally distributed at the nanoscale (100-200 nm) and exhibited a negative surface charge (-61.7 mV). Doxorubicin release from the nanocarrier persisted a long time (more than 300 hrs). PLD produced much higher tumor cell necrosis and less cardiotoxic effects than the other groups. The magnetic properties of the PLD nanocarrier make it an excellent material for hyperthermia [13].

The aim: enhance the therapeutic benefits resulted from the synergistic effect of Pegylated Liposomal Doxorubicin in a dose-dense regimen and Local mild Magnetothermy (Hyperthermy) electromagnetic field effect against chemoresistant advanced breast cancer.

MATERIALS AND METHODS

The competent ethics committee of the State non-commercial entertainment "National Cancer Institute of Ukraine" approved this study on December 12, 2023, under the number 249/2. This study adhered to the Declaration of Helsinki and the Good Clinical Practice Guidelines. All patients provided consent for the use of their health-related data for research reasons.

The study included 43 patients with chemoresistant advanced breast cancer; First group: 23 patients, who received a PLD 50 mg/m^2 and regional inductive mild hyperthermia treatment every four week (standard regimen); second group: 20 patients, who received PLD 50 mg/m^2 and regional inductive mild hyperthermia treatment every 2 week (dose-dense regimen).

Regional inductive mild hyperthermia employed electromagnetic fields at an effective frequency of 27.17±0.16 MHz and a peak power of 75 W. Treatment outcomes were evaluated using computed tomography and ultrasound imaging.

The MagTherm applicator (Radmir, Kharkiv, Ukraine) was placed in the tumor region to create the greatest intensity of electromagnetic irradiation, as determined by the Specific Absorption Rate (SAR) and temperature. Temperatures were controlled using fiber optic thermometers TM-4 (Radmir, Kharkiv, Ukraine). During the 30 min treatment session, the temperature rise that covered more than 90% of the area exposed to electromagnetic irradiation did not surpass 40°C. Prior to magnetothermy sessions, treatment plans were developed using CT scans.

Three weeks after the end of the treatment, the patients were sent for mammography, axilography and ultrasound diagnostics to evaluate the effectiveness of the treatment of metastases. increased the therapeutic effect of chemotherapy but also testified to the effect on the surrounding tissues and the primary malignant tumor of the breast gland, to which the therapeutic effect of magnetothermy (hyperthermy) was also directed.

Statistics

Patients who were alive or had no illness progression at trial closure were censored as of the most recent follow-up date and the Final Proportion of Viable Tumor Tissue (FPVCT) was used to describe early therapeutic effect analysis (chemosensitivity vs chemoresistance), which included patients who had received at least two doses of PLD and undergone at least one efficacy evaluation. Kaplan-Meier analysis was used to determine the results and 95% Confidence Intervals (CIs) were calculated. Two-sided p-values were reported and $p<0.05$ were considered significant.

RESULTS

The averaged statistical data, describing pathomorphosis in both groups, who received PLD in various regimens, were utilized to compute the final proportion of viable tumor tissue (FPVCT).

Patients with chemosensitivity (65.12%) reported significantly greater levels of chemotherapy-related variables compared to those with chemoresistance (34.88%), with $p = 0.0014$ (Figure 1a).

When PLD was given for the second group, chemosensitivity was higher than when given for the first group (15 patients or 75.00% vs. 13 patients or 56.52% respectively; $p = 0.038$) (Figure 1b).

But, when PLD was given for the first group, chemoresistance was higher, than when given for the second group (10 patients or 43.48% vs. 5 patients or 25.00% respectively, $p = 0.023$) (Figure 1b).

The quality of life for patients with resistant ABC who received combined RIMH and liposomal chemotherapy in standard and dose-dense regimens are equally (Table 1).

DISCUSSION

A previous trial revealed that a chemotherapy dose-dense regimen improved early clinical efficacy for advanced breast cancer patients, perhaps reducing time to surgery and improving overall survival, like in our investigation [14].

A phase II clinical investigation compared the efficacy of PLD to traditional methods in conjunction with Periwinkle alkaloids vinorelbine as a first-line therapy for metastatic BC. The study discovered that there were not any substantial variations in ORR, PFS, or OS among the two groups [15].

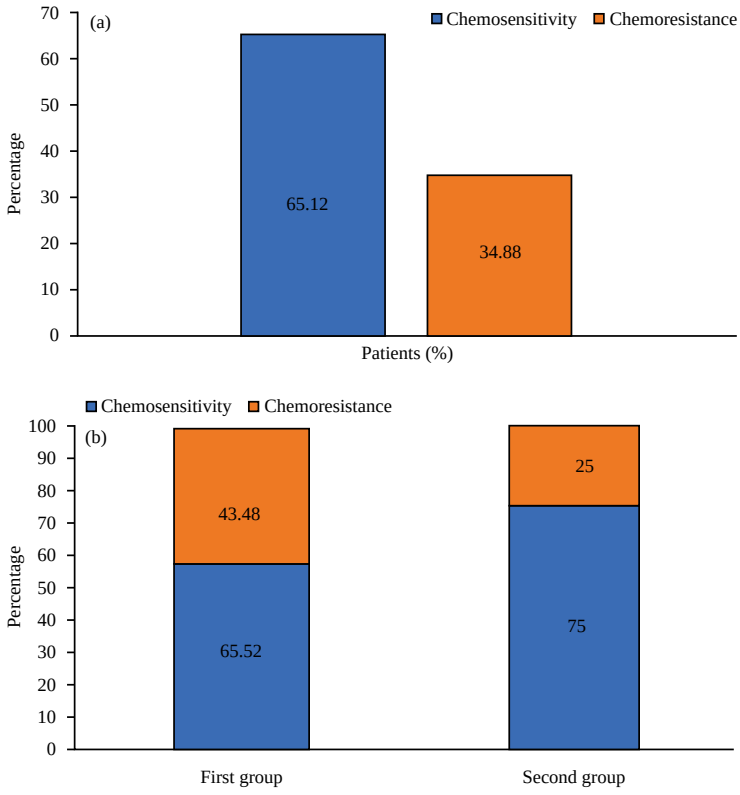

Figure 1(a-b): Dynamics of chemosensitivity and chemoresistance- final Proportion of Viable Tumor Tissue (FPVCT)

Table 1: Treatment-related toxicity in both groups

Adverse events	First group, cases (n) ----------Grade 1-2----------	Second group, cases (n)	p-value
Neutropenia	1	1	0.243
Nausea	2	2	0.003
Vomiting	1	0	0.034
Diarrhea	3	0	0.196
Hypersensitive	1	1	0.008
Cardiotoxicity	None	None	

Neutropenia, nausea, vomiting, diarrhea in both PLD groups did not have significantly distinction

Through improved permeability and retention, surface changes and endocytosis, liposomes are able to target tumors and reverse medication resistance [16].

For recurrent BC, the highest tolerable dosage was 50 mg/m^2 when the low-temperature PLD was combined with mild local hypertherapy [17], which also coincides with the result of this work.

In contrast to our result, Menyhárt *et al.* [18] documented that chemosensitivity had an insignificant effect on BC recurrence (17.3% in patients with anthracycline-resistant disease vs. 24.9% in non-anthracycline-resistant patients, $p = 0.027$). This could be due to different definitions of the chemosensitivity between two studies; they defined anthracycline resistance when patients had disease progression on non-anthracycline therapy.

Kaur I et colleagues discovered that combining Regional Inductive Mild Hyperthermia (RIMH) with chemotherapy improves treatment results for ABC patients at moderate temperatures of ~38-39°C. The combination therapy resulted in regression (30%) and disease stability (50% of patients) [19].

The simultaneous administration of liposomal pegylated drugs with magnetothermy in the comprehensive treatment of BC patients did not lead to negative changes in hemogram indicators or biochemical blood indicators, nor did it lead to the development of complications that had a significant impact on patients' general condition. The combination of liposomal pegylated drugs with magnetothermy (hyperthermy) greatly enhanced the immediate outcomes of treatment: The number of instances of process stability increased by 24.18% and the number of cases of partial regression increased by 10.8% [20].

Anthracyclines shown a high degree of activity in BC patients, various ways for designing regimens were devised, including the so-called dose-dense regimen, which uses liposomal anthracyclines in conjunction with magnetothermy (hyperthermia) and will be studied further.

CONCLUSION

Achieving a quicker clinical response for chemoresistant advanced breast cancer with a PLD dose-dense regimen while minimizing side effects and adverse responses. The complex employment of magnetothermy and pegylated liposomal medicines resulted in synergy of their anticancer action, which allowed to devitalize the tumor parenchyma of breast carcinoma.

REFERENCES

1. Anand, Uttpal, *et al.* "Corrigendum to 'cancer chemotherapy and beyond: Current status, drug candidates, associated risks and progress in targeted therapeutics' [genes & diseases 10 (2023) 1367–1401]." *Genes & Diseases,* vol. 11, no. 4, July 2024,. http://dx.doi.org/10.1016/j.gendis.2024.101211.
2. Yi, Wenzhe, *et al.* "Smart drug delivery systems to overcome drug resistance in cancer immunotherapy." *Cancer Biology & Medicine,* vol. 20, no. 4, May 2023, pp. 248-267. http://dx.doi.org/10.20892/j.issn.2095-3941.2023.0009.
3. Szlasa, Wojciech, *et al.* "Lipid composition of the cancer cell membrane." *Journal of Bioenergetics and Biomembranes,* vol. 52, no. 5, July 2020, pp. 321-342. http://dx.doi.org/10.1007/s10863-020-09846-4.
4. Fulton, Melody D., and Wided Najahi-Missaoui. "Liposomes in cancer therapy: How did we start and where are we now." *International Journal of Molecular Sciences,* vol. 24, no. 7, April 2023,. http://dx.doi.org/10.3390/ijms24076615.
5. Dadpour, Saba, *et al.* "The role of size in pegylated liposomal doxorubicin biodistribution and anti tumour activity." *IET Nanobiotechnology,* vol. 16, no. 7, August 2022, pp. 259-272. http://dx.doi.org/10.1049/nbt2.12094.
6. Hung, Chih Chiang, *et al.* "The efficacy of pegylated liposomal doxorubicin-based neoadjuvant chemotherapy in breast cancer: A retrospective case-control study in Taiwan." *Biochemistry Research International,* vol. 2020, April 2020, pp. 1-9. http://dx.doi.org/10.1155/2020/5729389.
7. Globus, Opher, *et al.* "The neoadjuvant systemic treatment of early breast cancer: A narrative review." *Annals of Breast Surgery,* vol. 7, no. 30, December 2023, pp. 39-39. http://dx.doi.org/10.21037/abs-21-109.
8. Castro-Torres, Jorge L, *et al.* "Development of handheld induction heaters for magnetic fluid hyperthermia applications and *in-vitro* evaluation on ovarian and prostate cancer cell lines." *Biomedical Physics & Engineering Express,* vol. 9, no. 3, March 2023,. http://dx.doi.org/10.1088/2057-1976/acbeaf.
9. Xu, Aoshu, *et al.* "Progressive study on the non-thermal effects of magnetic field therapy in oncology." *Frontiers in Oncology,* vol. 11, March 2021,. http://dx.doi.org/10.3389/fonc.2021.638146.
10. Volodimirovich, Movchan Oleksii, *et al.* "Advanced chemoresistant luminal B breast cancer patients' treatment improvement by a combination of liposomal pegylated doxorubicin and local Magnetothermy (regional inductive mild hyperthermia) compared to dose-dense therapy and local Magnetothermy (regional inductive mild hyperthermia)." *International Journal of Chemical and Biochemical Sciences*, vol. 24, no. 6, 2023, pp. 597-605. https://www.iscientific.org/volume-24-2023/
11. NCCN. *Guidelines for Treatment of Cancer by Type*. Breast Cancer. Version 4. 2024. https://www.nccn.org/guidelines/recently-published-guidelines
12. Syvak L. et al. "Magnetothermy of malignant neoplasms." *Clinicaloncology*, vol. 2, no. 26, 2017, pp. 66-70. https://www.clinicaloncology.com.ua/wp/wp-content/uploads/2017/07/614.pdf
13. Yazdan, Mostafa, *et al.* "Liposomal nano-based drug delivery systems for breast cancer therapy: Recent advances and progresses." *Anti-Cancer Agents in Medicinal Chemistry,* vol. 24, no. 12, July 2024, pp. 896-915. http://dx.doi.org/10.2174/0118715206293653240322041047.

14. Matikas, Alexios, *et al.* "Tailored Dose-Dense Versus Standard Adjuvant Chemotherapy for High-Risk Early Breast Cancer: End-of-Study Results of the Randomized PANTHER Trial." *Journal of Clinical Oncology*, vol. 42, no. 26, 2024, pp. 3077 - 3082. https://news.ki.se/improved-survival-for-breast-cancer-patients-with-dose-dense-chemotherapy
15. Decker, Thomas, *et al.* "Victoria: A randomised phase ii study to compare vinorelbine in combination with the mtor inhibitor everolimus versus vinorelbine monotherapy for second-line chemotherapy in advanced her2-negative breast cancer." *Breast Cancer Research and Treatment,* vol. 176, no. 3, May 2019, pp. 637-647. http://dx.doi.org/10.1007/s10549-019-05280-2.
16. Nel, Janske, *et al.* "Functionalized liposomes for targeted breast cancer drug delivery." *Bioactive Materials,* vol. 24, June 2023, pp. 401-437. http://dx.doi.org/10.1016/j.bioactmat.2022.12.027.
17. Aloss, Kenan, and Peter Hamar. "Recent preclinical and clinical progress in liposomal doxorubicin." *Pharmaceutics,* vol. 15, no. 3, March 2023,. http://dx.doi.org/10.3390/pharmaceutics15030893.
18. Menyhárt, Otília, *et al.* "Resistance to combined anthracycline–taxane chemotherapy is associated with altered metabolism and inflammation in breast carcinomas." *International Journal of Molecular Sciences,* vol. 25, no. 2, January 2024,. http://dx.doi.org/10.3390/ijms25021063.
19. Kaur, Ishdeep, *et al.* "Combination of chemotherapy and mild hyperthermia using targeted nanoparticles: A potential treatment modality for breast cancer." *Pharmaceutics,* vol. 15, no. 5, April 2023,. http://dx.doi.org/10.3390/pharmaceutics15051389.
20. Prieto-Callejero, Blanca, *et al.* "Relationship between chemotherapy-induced adverse reactions and health-related quality of life in patients with breast cancer." *Medicine,* vol. 99, no. 33, August 2020,. http://dx.doi.org/10.1097/md.0000000000021695.